# **FDA Executive Summary**

# Molecular and Clinical Genetics Panel March 8 & 9, 2011

FDA is convening this two-day meeting to seek the Panel's expert opinion and input on scientific issues concerning Direct to Consumer (DTC) genetic tests that make medical claims. <sup>1</sup>

This meeting is focused specifically on issues regarding clinical genetic tests that are marketed directly to consumers (DTC clinical genetic tests), where a consumer can order tests and receive test results without the involvement of a clinician.

The meeting will <u>not</u> address: clinical genetic testing in general (definitions in Appendix); DTC genetic tests that do not carry medical claims, such as genealogical or forensic tests; or privacy issues, including what may happen with the data collected and stored by DTC testing companies.

# **Background:**

Over the last two decades, driven in large part by the Human Genome Project, we have witnessed a rapid expansion in development and availability of new genomic technologies, resulting in an increasingly better understanding of genetic factors influencing human health and disease. Scientists have discovered hundreds of gene variations that are associated with human illness and patients' responses to treatments, and some genes or variations that may be targeted to develop effective treatments. Numerous molecular diagnostic tests have been developed based on genetic variations that are known or believed to contribute to a disease or that can help select appropriate treatment. FDA's regulatory challenge is to assure that benefits of this work may be appropriately delivered to patients and consumers, while ensuring that risks are appropriately managed.

During the last decade, FDA has approved or cleared a number of prescription use clinical diagnostic tests that assess genetic variation. These include carrier screening tests for hereditary diseases, tests to predict risk for future development of disease or recurrence of already diagnosed disease, and tests for prediction of treatment response.

In recent years, tests for numerous genetic variations with clinical implications have been introduced to the market as "DTC testing" (also called "direct-to-consumer genetic testing", "DTCG testing", or "direct access testing"), allowing a patient to order a test and receive results directly from the test offerer, rather than through the traditional means of physician ordering and receipt of indicated test results, with subsequent transmittal to

<sup>&</sup>lt;sup>1</sup> Brower V. FDA To Regulate Direct-to-Consumer Genetic Tests. JNCI Advance Access published October 21, 2010

<sup>&</sup>lt;sup>2</sup> Hamburg MA, Collins FS. Perspective: The Path to Personalized Medicine. N Engl J Med (2010) 363:301-304.

the patient, and follow-up care as needed. The DTC model for offering tests has created public health and social quandaries, where tests that predict drug response, tests that predict serious future health risks, and tests that provide preliminary findings of genotype-phenotype associations are now available to persons ordering their own testing. While this may enable the consumer to learn more about themselves, it also raises important questions of whether there is sufficient information available to assure that associations are real and meaningful, to which populations the results apply (and do not apply), and whether the technical tests used to measure the underlying genetic changes are accurate and reproducible. It also raises questions of how direct to consumer access might alter consumers' perceptions and behaviors about their own health and medical care, 3,4,5 either positively or negatively, and whether the availability of these tests directly to a general public of varying health literacy, without the involvement of a health care provider, has appropriate informational content. 6,7,8

DTC clinical genetic tests are similar in several ways to home use medical tests (see below). Yet unlike home use medical tests, many DTC clinical genetic tests often carry a disclaimer stating that they are intended for "educational and informational" purposes, and that the individual receiving the test results may wish to take them to their clinician for follow-up.

Home use tests are tests that are used at home by untrained persons without the help of a healthcare professional. FDA regulates home use tests as medical devices. Home use tests could be generally divided in two different types - *collection kits* and *test kits*. Characteristics of each of these two test types are as follows:

- a) For home use *collection kits*:
  - Specimen is collected by the test subject and mailed to a laboratory;
  - Test is performed, read and interpreted by a trained lab professional in a certified laboratory;
  - Results are provided over the phone, the internet or in the mail; live counseling may be available.

FDA has approved several HIV and Hepatitis C virus infection tests with home use *collection kits*.

- b) For home use *test kits*:
  - Specimen is collected by the test subject;

<sup>3</sup> Bloss CS, Schork NJ, Topol EJ. Effect of Direct-to-Consumer Genomewide Profiling to Assess Disease Risk. N Engl J Med. (2011) Jan 12. [Epub ahead of print]

<sup>&</sup>lt;sup>4</sup> Sanderson SC, Wardle J. Will genetic testing for complex diseases increase motivation to quit smoking? Anticipated reactions in a survey of smokers. Health Educ Behav. 2005 32:640-53.

<sup>&</sup>lt;sup>5</sup> Kaufman D, Murphy Bollinger J, Devaney S, Scott J. Direct from consumers: A survey of 1,048 customers of three direct-to-consumer personal genomic testing companies about motivations, attitudes, and responses to testing. Abstract number 390, 2010 Annual Meeting, The American Society of Human Genetics.

<sup>&</sup>lt;sup>6</sup> Lachance CR, Erby LA, Ford BM, Allen VC Jr, Kaphingst KA. Informational content, literacy demands, and usability of websites offering health-related genetic tests directly to consumers. Genet Med. (2010)

<sup>&</sup>lt;sup>7</sup> Stack CB, Gharani N, et al. Genetic risk estimation in the Coriell Personalized Medicine Collaborative. Genet Med. (2011) 13:131-139.

<sup>&</sup>lt;sup>8</sup> McBride CM. Wade CH, Kaphingst KA. Consumers' Views of Direct-to-Consumer Genetic Information. Annu. Rev. Genomics Hum. Genet. 2010. 11:427–46.

- Test is performed, read and interpreted by the test subject, so:
  - operator is "untrained" (no specific medical training)
  - live pre-test counseling and post-test counseling at the time the test result is provided is usually absent
  - Medical referral after particular test results is patient initiated.
  - In some cases the test includes collection devices and pre-paid mailer for free confirmatory testing such as in drugs of abuse.

FDA has cleared a number of home use test kits including some glucose, cholesterol, and pregnancy tests for home use.

DTC genetic tests effectively create a third type of home use tests. Similarly to home use collection kits, DTC tests utilize some type of at-home use collection device, and collected samples are sent to high complexity clinical laboratories where actual tests are performed. However, similarly to home use test kits, for DTC tests any medical referral is patient initiated and often no live pre-test or post-test counseling is sought or provided. This has raised questions including: whether consumers might undertake self-directed actions as a result of DTC test results<sup>3</sup>, such a changing or discontinuing prescribed medications; whether clinicians will rely on these test results to initiate medical action<sup>9</sup>, and whether a physician would order additional tests on the basis of DTC test results with unknown accuracy and reliability.

### **Regulatory Background:**

The FDA must, by regulation, rely upon valid scientific evidence to determine that a medical device is safe and effective. Valid scientific evidence is evidence from wellcontrolled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results. There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use 10. Risks of a medical test result are primarily related to consequences of false positive and false negative results.

10 21 CFR § 860.7

<sup>&</sup>lt;sup>9</sup> Plon SE, Parks B, et al. Are physicians prepared to effectively use genetic testing for at-risk relatives of cancer patients? Abstract number 149, 2010 Annual Meeting, The American Society of Human Genetics.

# **Issues to Address:**

Currently, FDA cleared or approved prescription clinical genetic tests have very specific claims, and analytical and clinical performance (e.g., accuracy, precision). FDA cleared or approved tests that are being offered directly to consumers (e.g., OTC), must meet certain pre-defined user performance thresholds designed to mitigate or prevent misuse and misinterpretation.

FDA would like to receive the Panel's input on the following issues:

- The risks and benefits of making clinical genetic tests available for direct access by a consumer without the involvement of a clinician (i.e., without a prescription). The discussion will include consideration of the benefits and risks of direct access for different tests or categories of tests that might suggest differences in the regulatory approach. Clinical genetic test categories that have been proposed to be offered directly to consumers include:
  - O Genetic carrier screening for hereditary diseases (e.g., cystic fibrosis carrier screening);
  - Genetic tests to predict risk for future development of disease in currently asymptomatic persons (e.g., tests to predict risk of developing breast or ovarian cancer); and
  - O Genetic tests for treatment response prediction (e.g., tests to predict whether individual will respond to a specific drug or course of therapy).
- The risks of and possible mitigations for incorrect or misunderstood test results for clinical genetic tests offered through direct access testing, without live counseling.
- The level and type of scientific evidence appropriate for supporting direct-toconsumer genetic test claims including whether the evidence levels should be different than those required to support similar claims for prescription use (i.e. ordered through a clinician) clinical genetic tests.

In accompanying material, we are including a list of currently offered DTC genetic tests (list is not all-inclusive), compiled from the web sites of several companies offering this type of test (Appendix 2). As additional reference, since it lists and defines different categories of DTC genetic testing, "A Common Framework of Principles for direct-to-consumer genetic testing services" published by UK Human Genetics Commission (HGC) in 2010 is also provided as a reference. <sup>11</sup> This document, divides DTC genetic testing in 11 categories, some of which have medical purpose, and others that do not (Table 1, page 2-3 of the HGC document).

\_

<sup>&</sup>lt;sup>11</sup> A Common Framework of Principles for direct-to-consumer genetic testing services, UK Human Genetics Commission (2010)

#### **APPENDIX 1:**

#### **Genetic Tests Definitions**

- A genetic test is the analysis of human DNA, RNA, chromosomes, proteins, or certain metabolites in order to detect alterations related to a heritable disorder. This can be accomplished by directly examining the DNA or RNA that makes up a gene (direct testing), looking at markers co-inherited with a disease-causing gene (linkage testing), assaying certain metabolites (biochemical testing), or examining the chromosomes (cytogenetic testing).<sup>12</sup>
- Clinical tests are those in which specimens are examined and results reported to the provider or patient for medical purposes, such as <u>diagnosis</u>, <u>prevention or treatment</u>, in the care of individual patients.
  - United States laboratories performing clinical tests must be CLIA certified.
  - Test results are reported in writing.
- Research tests are those in which specimens are examined for the purpose of gaining fundamental scientific knowledge, or for early stage development of a clinical test.
  - Laboratories performing only research testing are not subject to CLIA regulations.
  - Research test results are generally not reported to patients or their providers.
- Genetic tests that do not carry medical claims, such as ancestry or forensic tests, are not under the FDA's medical device oversight.

#### **DTC Genetic Tests**

- Genetic tests marketed and offered directly to consumers, or DTC genetic tests, are currently a small part of the broader category of genetic tests.
- DTC genetic tests are similar in several ways to home use medical tests that are used by an untrained person without the help of a health care professional. Some of the home use tests involve the at-home collection of a specimen (blood, urine) that is then sent to a clinical laboratory to analyze the samples. Medical referral may be initiated by the patient upon obtaining a certain test result, and medical counseling is typically not provided to patients.

# FDA clearance or approval<sup>13</sup>

FDA classifies medical devices, including diagnostic tests, into one of three classes. Classification identifies the level of regulatory control that is necessary to assure the safety and effectiveness of a medical device. The classification will identify the regulatory pathway (exempt from premarket submission, premarket notification [510(k)] or premarket approval (PMA)) required to obtain FDA clearance/approval for marketing.

(http://www.ncbi.nlm.nih.gov/projects/GeneTests/static/concepts/primer/primerwhatistest.shtml).

13

http://www.fda.gov/medicaldevices/products and medical procedures/device approvals and clearances/default.htm

<sup>&</sup>lt;sup>12</sup> GeneTests.org

A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is substantially equivalent (SE), (that is, as safe and effective as a legally marketed device that is not subject to premarket approval (PMA)). If found to be substantially equivalent, a device receives *clearance* for marketing. 510(k) (premarket notification) to FDA is required at least 90 days before marketing unless the device is exempt from 510(k) requirements.

Premarket Approval (PMA) is the most stringent type of device marketing application required by FDA. A PMA is an application submitted to FDA to request *approval* to market. Unlike premarket notification, PMA approval is to be based on a determination by FDA that the PMA submission contains sufficient valid scientific evidence to provide a reasonable assurance that the device is safe and effective for its intended use or uses.

# In vitro Diagnostics (IVD)

In vitro diagnostic devices are defined to include "...those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae." <sup>14</sup>.

# **Clinical Laboratory Improvement Act (CLIA)**

The Centers for Medicare & Medicaid Services (CMS) oversees all laboratories providing testing (except research) performed on U.S. citizens through the Clinical Laboratory Improvement Amendments (CLIA)<sup>15</sup>. CLIA oversees quality of laboratory testing and an accreditation program for clinical laboratories.

\_

<sup>&</sup>lt;sup>14</sup> 21 CFR § 809.3

<sup>15</sup> http://www.cms.gov/clia/